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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/724,983	11/28/2000	Scott A. Waldman	TJU-2444	8378

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EXAMINER	
YAO, LEI	

ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/724,983	WALDMAN, SCOTT A.	
	Examiner	Art Unit	
	Lei Yao, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23,28-30,36 and 50-89* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23,28-30,36 and 50-89* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

REQUEST FOR CONTINUED EXAMINATION

It is acknowledged that the renewed petition filed August 23, 2006 is granted. The request filed on 8/23/06 for a Continued Examination (RCE) under 37 CFR 1.114 based on Application No. 09724983 is acceptable, and a RCE has been established. An action on the RCE follows.

Claims 1-22, 24-27, 31-35, 37-49 are cancelled. Claims 81-89 are added. Claims 23, 28-30, 36 and 50-89 are pending and under consideration

Information Disclosure Statement

The information disclosure statement (s) (IDS) submitted on 7/28/2003 and 8/23/2006 are/is considered by the examiner and initialed copies/copy of the PTO-1449 are/is enclosed.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 23, 28-30, 36, and 50-89 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims are indefinite because the term "a therapeutically effective amount of pharmaceutical composition or conjugated compound that comprise an ST receptor ligand wherein said ST receptor ligand is an antibody, Fab or $F(AB)_2$" in claim 23, 63, and 81 is not clear.

MPEP2173.05 state:

> *The common phrase" an effective amount" may or may not be indefinite. The proper test is whether or not one skilled in the art could determine specific values for the amount based on the disclosure.*
>
> *The phrase "an effective amount" has been held to be indefinite when the claim fails to state the function which is to be achieved and more than one effect can be implied from the specification or the relevant art. In re Fredericksen 213 F.2d 547, 102 USPQ 35 (CCPA 1954).*

The specification on page 37 teach that "A therapeutically effective amount" is an amount which is effective to cause a cytotoxic or cytostatic effect on metastasized colorectal cancer cells without

causing lethal side effects on the individual. However it does not teach what has been achieved in the treatment or whether the amount of the antibody used in the treatment is "therapeutically effective amount". Therefore, the metes and bounds of "a therapeutically effective amount" in claims 23 and 63 cannot be determined because those skilled in the art would not be able to determine the therapeutically effective amount of the ST receptor antibody used for claimed method. Claims 23 and 63 also render the dependent claims indefinite.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 23, 28-30, 36, and 50-89 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are drawn to a method of treating an individual suspected of suffering, or suffering from metastatic colorectal cancer comprising the step of administering to individual pharmaceutical composition comprising an active agent comprising 5-fuorouracil and an ST receptor antibody, Fab or $F(AB)_2$. To satisfy the requirement of 112, 1st paragraph, it is necessary that the specification provides an enabling disclosure of how to make and use a claimed invention. The method objective of claims is a method of treating a colorectal cancer with a composition comprising an antibody to ST receptor. Thus, it

would be expected that one of skill in the art would be able to treat the cancer with any antibody to receptor without undue experimentation by using the claimed method.

The specification teaches heat stable toxin referred as ST or ST receptor binding peptide or ST peptide (page 13). The specification teaches ST receptors are unique in that they are only localized in the apical brush border membranes of the cells lining the intestinal tract (bridge pate of 9-10). The specification teaches Guanylin, a 15 amino acid peptide, has about 50% sequence homology to ST and binds to ST receptor and activates guanylate cyclase (page14). The specification further teaches that an assay may be use to determine whether or not the peptides are ST receptor ligands comprising incubating a preparation of ST receptor (intestinal membranes from rat or human intestine or the cells, page 17). However, the specification does not provide teachings on A) the detailed information about the ST receptor expressed in the colorectal cancer cells comprising structure or sequence; B) antibody to the ST receptor interacting with the ST receptor on colorectal cancer; C) the method of treating any cancer with the composition comprising antibody to the ST. Thus, the specification invites the skilled artisan to experiment to determine how to use the claimed composition comprising an ST receptor antibody or the Fab or F(ab)2 to treat metastatic colorectal cancer does not set forth sufficient teachings to allow one skilled in the art to practice treating such cancer. There are no working examples to guide or assist the skilled artisan in practicing the claimed method of treating metastatic colorectal cancer with antibody or antibody fragment in combination with other active agent. In addition, although the specification cites a few references (page 15) teaching the ST binding, non of the references identify or teach the ST receptor. For example, a cited reference, (Okamoto, Infec and Immun vol 55, page2121-2125, 1987), on line 32 of page 15, teaches that ST receptor is separable from guanylate cyclase indicating that the receptor is coupled to the activation of guanylatd cyclase (page 2124, col 1 and cited reference 11, abstract) and reference does not suggest or teach what the receptor is. Thus, one skilled in the art and specification did not seem have identified the ST receptor with a sequence expressed on colorectal cancer cells at the time of filing instant application. Therefore, the specification provides insufficient guidance or direction to predictably enable one of ordinary skill in the art to use the claimed invention to treat colorectal cancer with composition or conjugate comprising antibody to ST receptor.

Moreover, those of skill in the art recognize the unpredictability of treating tumors with antibodies. The references have been discussed in the previous office action and again below.

Jain R. K. (Scientific American, 271(1): 58-65, July 1994) discloses the art known barriers to the delivery of drugs into solid tumors. These impediments include (1) Non-uniform blood delivery to all areas of the tumor in which some areas of the tumor receive therapeutic agents and other areas of the tumor receive no therapeutic agent at all. (Page 60 col. 3); (2) Increased viscosity of blood in the tumor itself which also hinders drug delivery to the tumor (see paragraph bridging pages 60 and 61); (3) High liquid pressures in the interstitial matrix can retard the delivery of large therapeutic agents, such as antibodies, into tumors (page 61, Col. 1 paragraph 1); (4) Convection is a necessary mechanism by which larger therapeutic molecules such as antibodies, reach target cells which are not directly fed by the vasculature. Convection is not observed in large tumors (defined as more than ½ centimeter in diameter, page 62 col. 1) and convection is necessary for adequate drug delivery of molecules having a molecular weight of more than 5000 (page 61, col. 1 through page 63, col. 3) and (4) Molecules as large as antibodies (i.e., MW=150,000) would require several months to reach a uniform concentration in a tumor that measures 1 centimeter in radius (page 63, col. 2). Further, Dillman R. O., (Annals of Internal Medicine, 111:592-603, 1989) summarizes (see abstract) the status of in-vivo use of monoclonal antibodies for treating cancer wherein despite advances in biotechnology, many major hurdles persist including tumor cell heterogeneity, lack of cytotoxicity, and the development of human anti-mouse antibodies (HAMA). Also, Weiner L. M. (Seminars in Oncology, 26 (4 Suppl 12):41-50, August 1999) provided an overview of monoclonal antibody therapy including some promising activity, however, major obstacles to clinical efficacy still exist extending the unpredictability of this treatment. This includes impaired distribution and delivery of antibody to the tumor site, inadequate trafficking of potential cellular effectors to tumor, antigenic heterogeneity, shed or internalized targets and insufficient target specificity (see page 43).

Furthermore, as disclosed by Dillman, R. O. [b] (Journal of Clinical Oncology, 12(7):1497-1515, 1994) discloses, after reviewing the literature on the use of unconjugated monoclonal antibodies to treat cancer, that "at present, there are no unconjugated monoclonal antibodies that have proven therapeutic benefit in hematologic malignancies or solid tumors." Thus, absent objective evidence to the contrary, it is highly unpredictable that applicant's unconjugated antibody would possess any therapeutic effects for colorectal cancer.

No direction or guidance is provided in current specification to assist one skilled in the art using a composition comprising an antibody to ST receptor or its fragment that in a method of treating colorectal cancer. In view of the lack of the predictability of the art to which the invention pertains as evidenced by the art above, one skilled in the art would be forced into under experimentation in order to practice the claimed invention.

Response to applicant argument

It is noted that the previous rejection of claims 23, 28-30, 36, and 50-80 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement for the method of treating metastatic colorectal cancer and response to the argument in the office action dated 11/22/2004 are maintained and have been recorded.

The response filed 8/23/2006 has been carefully considered but is deemed not to be persuasive. *Applicant argue that it is well settle that the Office has the initial burden of established that a claimed invention does not meet the enablement requirement and only upon meeting its burden does the burden shift to the applicants. Applicant argue again the references cited in the office action, especially the reference by Weiner about the encouragement, cutting-edge and valuable of antibody therapy and states that despite pointing out survival obstacles to be overcome in order to maximize clinical effectiveness of antibody therapy in cancer treatment..... which do not support a finding of non-enablement but rather are consistent with applicant assertion.* In response to this argument, the rejection under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, is based on whether one of skill in the art would be able to practice or use the claimed invention without undue experimentation. Cutting edged, encouraged, or valuable result is merely an invitation for the further research and experimentation, which could not be used for treating a patient without the consistent in vivo result achieved. Certainly, Weiner's reference offers encouragement and hope for one skilled in the art using antibody for treating a disease. However, encouragement and hope are not enough at this stage to form a patent that allows one skilled in the art to practice and use the claimed invention without undue experimentation.

Applicant further argues that the Dillman's reference was published before the application was filed. Applicant refers the sentence "trials of antibody alone and radiolabled antibodies have confirmed the feasibility of this approach" and states this does not support a finding of non-enablement but rather are consistent with applicant's assertion. In response to this argument, feasibility of approach is also encouraged result, as discussed above, merely is an invitation for the further research and experimentation, which could not be used for treating a patient without the consistent in vivo result achieved. Thus, Applicant's argument has not been found persuasive, and the rejection is maintained.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed.

Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

1. Claims 23, 28-30, 36, and 50-89 remain and/or are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 5, 9, 10, 28-31, and 54-58 of U.S. Patent No. 5,879,656. Although the conflicting claims are not identical, they are not patentably distinct from each other as stated in the previous office action and again below:

US Patent 5,879,656 ('656) claims a method of treating an individual suspected of suffering from "metastasized" colorectal cancer comprising administering said individual a therapeutically effective amount of pharmaceutical composition comprising conjugated compound comprising ST receptor ligand and an active moiety; wherein said active moiety is a radiostable active agent that is a radiostable therapeutic agent. (The patent defines radiostable as "compounds which do not undergo radioactive decay, i.e. compounds that are not radioactive (column 4, line 36)). The claims are further drawn to active agents are chemotherapeutic agents selected from the group consisting of 5-fluorouracil, melphalan, etc. The claims are further drawn to wherein said ST receptor binding moiety is an antibody, FAB, or F(Ab), and wherein said ST receptor ligand is an antibody. The claims are also drawn to wherein the composition is administered intravenously.

The currently pending claims are also drawn to a method of treating an individual suspected of suffering from colorectal cancer comprising administering to said individual a therapeutically effective amount of a pharmaceutical composition or conjugated compound comprising an ST receptor ligand, an active agent that causes cell death, and a pharmaceutically acceptable carrier or diluents. Thus, the claims of the '656 patent represent an obvious variation or species of the present claims in that the present claims encompass treating an individual suffering from a metastasized colorectal cancer. Also, there is no patentable distinction between radiostable agents and agents that cause cell death because the broadly claimed agents are considered radiostable and or cause cell death.

Response to applicant remark (8/23/2006)

Applicants have maintained their intention to file a Terminal Disclaimer (page 13), yet none have been provided. Thus, rejection is maintained and made again above for reason of the record.

2. Claims 23, 28-29, 58, 63-65, 76, 81, 82, and 85 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 6 and 8 of U.S. Patent No. 6060037 ('037) in view of de Sauvage et al., (JBC, vol 267, page 6479-6482, April, 1992).

US Patent '037 claims a method of treating an individual suspected of suffering from "metastasized" colorectal cancer comprising administering said individual a therapeutically effective

amount of pharmaceutical composition comprising conjugated compound comprising ST receptor binding moiety and an active moiety that cause cell death, wherein said active moiety is a radiostable active agent that is a radiostable therapeutic agent.

US Patent '037 do not teach that ST receptor binding moiety is antibody for ST receptor.

de Sauvage et al., teach antibodies directed to ST (heat stable receptor) (page 6481, figure 4).

The currently pending claims are also drawn to a method of treating an individual suspected of suffering from colorectal cancer comprising administering to an individual a therapeutically effective amount of a pharmaceutical composition or conjugated compound comprising a ST receptor ligand, an active agent that causes cell death, and a pharmaceutically acceptable carrier or diluents.

Thus, current pending application are drawn to the same method claimed by '037 patent in combination with the teaching of de Sauvage et al., because one of ordinary skill in the art at the time the invention was made would have been motivated to combine the teachings of the claims of US Patent '037 with the teaching of de Sauvage et al., to make a composition or a conjugated compound comprising the same active components comprising an antibody in order to directly bind to the ST receptor with the composition and increase a higher therapeutic efficiency. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success to use the antibody to ST receptor taught by Sauvage et al., in the composition or conjugated compound claimed in the US patent '037 because Sauvage et al., have shown that the antibody binds effectively to the ST receptor and claims in patent '037 are drawn to a composition comprising conjugated compound formed with ST receptor binding moiety and an active moiety that cause cell death. Therefore, the claims as whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lei Yao, Ph.D. whose telephone number is 571-272-3112. The examiner can normally be reached on 8am-6.00pm Monday-Thursday.

Any inquiry of a general nature, matching or file papers or relating to the status of this application or proceeding should be directed to Kim Downing for Art Unit 1642 whose telephone number is 571-272-0521

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Lei Yao,
Examiner
Art Unit 1642

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